PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2848-65-PCT	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US05/02325	International filing date (*day/month/year*) 24 January 2005 (24.01.2005)	(Earliest) Priority Date (*day/month/year*) 23 January 2004 (23.01.2004)
Applicant THE REGENTS OF THE UNIVERSITY OF COLORADO		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 10 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the Report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed.
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☒ **Certain claims were found unsearchable** (See Box No. II)
3. ☒ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the drawings to be published with the abstract is Figure No. 1
      ☒ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/02325

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 4-16, 19, 20 and 1-3 (in part), 17 (in part), 21-25 (in part)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-17 and 19-25

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/02325

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8): C12Q 1/70(2006.01),1/68(2006.01);G01N 33/53(2006.01),33/574(2006.01)
C07K 1/00(2006.01),16/00(2006.01);A61K 38/00(2006.01)

USPC: 435/4,6,7.1,7.23
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/4,6,7.1,7.23

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PGPUB, PATFULL, MEDLINE, EMBASE, BIOSIS, CAPLUS, TOXCENTER, DISSABS, DERWENT, PCTFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US Patent Application Publication 2003/0065156, 03 April 2003 (03.04.2003), paragraphs 004-007, 203, 113, 233-234, 288, 299	1, 3, 17
Y	US Patent Application Publication 2002/0102685 (Sibilia et al) 01 August 2002 (01.08.2002), paragraphs 0041.	1, 3, 17
A	Chen et al., US Patent No: 6,596,878, July 2003	1, 3, 17
A	Uckun et al , US Patent No. 6,355,678, 12 March 2002	1, 3, 17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
14 April 2006 (14.04.2006)

Date of mailing of the international search report
30 MAY 2006

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Form PCT/ISA/210 (second sheet) (April 2005)

Continuation of Box II Reason 2:
The claims, as written, are not fully supported by the description and the scope of the claims are broader than justified by the description and drawings.

Claims 4-16, 19 lack support that a gene or combination of genes comprising nucleic acid sequences represented by SEQ ID NO: 1-194 are overexpressed in patients with cancer and its correlation of the genes' overexpression with an EGFR-inhibitor, agonist, or a drug having similar biological activity would likely results in predictable therapeutic benefit.

Claim 2 lacks support in the specification for correlating the identification of a gene having a level of expression in EGFR inhibitor-sensitive cells that is statistically significantly different than the level of expresion of the gene or genes in EGFR inhibitor-resistance cells as potentially being a molecule that interacts with the EGFR pathway to allow or enhance responsiveness to EGFR inhibitors.

Claim 20 lacks support in the specification that a gene from ZEB1 or SIP1 showing differential expression in the presence of gefitinib would result in a benefitical therapeutic effect. Specifically, the nexus is absent and there are no controls to show that the differential expression could not have resulted from toxicity effects.

Claims 21-25 are indefinite because one cannot determined whether "the expression of a gene or genes" refer to the expression of the gene(s) in patient's tumor cells or the expression of the gene(s) that have been correlated with sensitivity or resistance to EGFR inhibitor. Additionally, Claims 21-25 lack support because the specification does not teach comparing the expression level of any gene(s) to noncancerous cell of the same type, to autologous, noncancerous cell from the patient, to gene(s) in a control cell that is resistant to the EGFR inhibitor, to gene(s) in a control cell that is sensitive to the EGFR inhibitor, or to control gene(s) expression levels that have been correlated with sensitivity and/or resistance to the EGFR inhibitor. In short, the specification does not teach any controls for comparison.

Claims 1, 3, 17 will only be examined in part, i.e., with respect to an "EGFR inhibitor," because the specification lacks support that an administration of an EGFR agonist or a drug having substantially similar biological activity as EGFR inhibitor could predictably have a therapeutic benefit.

Claims 1, 3, 17 will also be examined in part, i.e., with respect to the in vitro screening of an EGFR inhibitor because the specification lacks support for comparing the expression of the gene or genes in the patient's tumor cells that is stastistically more similar to the expression levels of the gene or genes and for correlating said expression levels with senstivity or resistance to the EGFR inhibitor.

The phrase "sensistive" is interpreted to mean responsive to an EGFR inhibitor and the term "resistance" is interpreted to mean not responsive to an EGFR inhibitor.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

1. Claims 1-17, 19-25, drawn to a method to select a cancer patient who is predicted to benefit from therapeutic administration of one component comprising providing a sample of tumor cells from a patient to be tested, detecting in the sample the expression of one gene wherein detection is detected by detecting a nucleic acid whose expression has been correlated with sensitivity or resistance to an EGFR inhibitor, comparing the level of expression of the gene, and selecting the patient as being predicted to benefit from therapeutic administration of the EGFR inhibitor.

NOTE: Claim 4 contains a permutation of amino acid sequences comprising SEQ ID NO: 1-194. These permutations represents a 194! factorial of sequence combinations. As such, Applicant is required to choose ONE combination from 1.33 x 10 exp (361) permuations. Applicant is reminded that any combinations not represented by the elected combination will be withdrawn as being drawn to non-elected inventions.

2. Claims 1-15, 18, drawn to a method to select a cancer patient who is predicted to benefit from therapeutic administration of one component comprising providing a sample of tumor cells from a patient to be tested, detecting in the sample the expression of one gene wherein detection is detected by detecting a protein production whose expression has been correlated with sensitivity or resistance to an EGFR inhibitor, comparing the level of expression of the gene, and selecting the patient as being predicted to benefit from therapeutic administration of the EGFR inhibitor.

NOTE: Claim 4 contains a permutation of amino acid sequences comprising SEQ ID NO: 1-194. These permutations represents a 194! factorial of sequence combinations. As such, Applicant is required to choose ONE combination from 1.33 x 10 exp (361) permuations. Applicant is reminded that any combinations not represented by the elected combination will be withdrawn as being drawn to non-elected inventions.

3. Claim 26, drawn to a method to identify molecules that interact with EGFR pathway to allow or enhance responsiveness to EGFR inhibitors comprising providing a sample of cells that are sensitive or resistant to treatment with gefitinib, detecting the expression of at least oen gene in the gefitnib sensitive cells as compared to the lvel fo expression fo the gene in the gefittinib.

4. Claims 27-39, claims to a plurality of polynucleotides for the detection of the expression of genes that are indicative of sensititivy or resistance to gefitinib.

Species Election

The invention of group 1 contains multiple generic claims that include a plurality of alternatively usable substances or members. These alternative limitations are independent or distinct inventions such that they do not share a common utility or share a substantial structural feature disclosed as being essential to that utility. Because they are not so closely related, a search and examination of the entire claim cannot be made without undue burden. The members of the alternative groupings are described in the following:

Group 1 is generic to a plurality of disclosed patentably distinct species comprising the following therapeutic administrations: EGFR inhibitor, EGFR inhibitor agonist, and a drug having substantially similar biological activity as EGFR inhibitor (Claim 1). These species represent separate and distinct therapeutic administrations with different structures and functions such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Additionally, group 1 is generic to a plurality of disclosed patentably distinct species comprising the following genes: comprising ONE sequence selected from SEQ ID NO: 1-194 (Claims 4, 19), ZEB1 (Claim20), SIP1 (Claim 21). These species represent separate and distinct molecules with different structures and functions such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Additionally, Group 1 is generic to a plurality of disclosed patentably distinct species comprising the following comparison methods: comparing the expression of one gene to the gene in a cell from a non-cancerous cell of the same type (Claim 21), in an autologous noncancerous cell (Claim 21), in a control cell that is resistant to EGFR inhibitor (Claim 23), in a control cell that is sensitive to the EGFR inhibitor (Claim 24). These species represent separate and distinct methods with different objectives, reagents, population samples, and methodologies such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

Applicant is required to elect a single disclosed species for examination.

Rule 13.1 of the Patent Cooperation Treaty (PCT) states that an international application should relate to only one invention or to a group of inventions if all inventions are so linked as to form a single inventive concept; i.e., if there is unity of invention. According to Rule 13.2, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The term "special technical features" is referred to as those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art (Rule 13.2). The determination is made on the contents of the claims as interpreted in light of the description and drawing (if any). If there is no special technical feature or if multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(d).

The inventions listed as groups 1-4 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature linking groups 1-3 appears to be a method to select a cancer patient who is predicted to benefit from therapeutic administration of an EGFR inhibitor.

However, the technical feature linking groups 1-4 appeared to have been taught by other(s). For example, Chen et al. (US Patent No: 6,596,878, July 2003) teach a method for screening inhibitor compounds of EGFR or HER2 (col 3, lines 39-41) with for appropriate administration to an animal or human (col 28, lines 6-10). Specifically, Chen et al. teach EGFR inhibitors have different selectivity in inhibiting the activity of a receptor tyrosine kinase and thus the EGFR inhibitors are selected by measuring growth of cells containing the receptor tyrosine kinase (col 8, lines 56-65). Further, Chen specifically teaches that the EGFR driven disorder are characterized by over-expression of EGFR and that the production of a level of HER2 activity is correlated with a cell proliferative disorder (i.e., as the level of EGFR increases, the severity of the cell proliferative disorder increases) (bridging paragraph col 21-22). The method of the prior art comprises the same method steps as claimed in the instant invention, that is, screening for selecting a patient as being predicted to benefit from therapeutic administration of the EGFR inhibitor. Thus the claimed method is anticipated because the method will inherently lead to correlating the level of expression of genes detected in the patient sample. See Ex Parte Novitski 26 USPQ 1389 (BPAI 1993).

The technical feature linking the inventions of groups 1-4 does NOT constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art. Therefore, restriction for search purpose is proper.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/02325